

We claim:

1. A mixture of recombinant cells, each cell of which comprises:

- (i) an expressible recombinant gene encoding a heterologous receptor protein whose signal transduction activity is modulated by interaction with an extracellular signal; and
- (ii) an expressible recombinant gene encoding a heterologous potential receptor effector polypeptide,

wherein collectively the mixture of cells expresses a variegated population of said receptor effector polypeptides, and modulation of the signal transduction activity of the receptor protein by a test polypeptide provides a detectable signal.

2. A mixture of recombinant cells, each cell of which comprises:

- (i) a heterologous receptor protein whose signal transduction activity is modulated by interaction with an extracellular signals;
- (ii) an expressible recombinant gene encoding a heterologous potential receptor effector polypeptide; and
- (iii) a reporter gene construct containing a reporter gene in operative linkage with one or more transcriptional regulatory elements responsive to the signal transduction activity of the receptor protein,

wherein collectively the mixture of cells expresses a variegated population of test polypeptides as receptor effectors.

3. The cells of claim 2, wherein the receptor is a nuclear receptor.

4. The cells of claim 2, wherein the receptor is a cell surface receptor.

5. A mixture of recombinant cells, each cell of which comprises:

- (i) a receptor protein whose signal transduction activity is modulated by interaction with an extracellular signals;
- (ii) an expressible recombinant gene encoding a heterologous potential receptor effector polypeptide; and
- (iii) a reporter gene construct containing a reporter gene in operative linkage with one or more transcriptional regulatory elements responsive to the signal transduction activity of the receptor protein,

wherein collectively the mixture of cells expresses a variegated population of test polypeptides as receptor effectors.

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6. The cells of claim 5, wherein the receptor is a nuclear receptor.
7. The cells of claim 5, wherein the receptor is a cell surface receptor.
8. A mixture of recombinant cells, each cell of which comprises:
  - (i) a cell surface receptor protein whose signal transduction activity is modulated by interaction with an extracellular signal; and
  - (ii) an expressible recombinant gene encoding a heterologous potential receptor effector polypeptide including a signal sequence for secretion,wherein collectively the mixture of cells expresses a variegated population of test polypeptides as receptor effectors, and modulation of the signal transduction activity of the receptor protein by a test polypeptide provides a detectable signal.
9. The recombinant cells of claim 8, wherein each cell further comprises a reporter gene construct containing a reporter gene in operative linkage with one or more transcriptional regulatory elements responsive to the signal transduction activity of the cell surface receptor protein, expression of the reporter gene providing the detectable signal.
10. The recombinant cells of claim 8, wherein the reporter gene encodes a gene product that gives rise to a detectable signal selected from the group consisting of: color, fluorescence, luminescence, cell viability relief of a cell nutritional requirement, cell growth, and drug resistance.
11. The recombinant cells of claim 9, wherein the reporter gene encodes a gene product selected from the group consisting of chloramphenicol acetyl transferase, beta-galactosidase and secreted alkaline phosphatase.
12. The recombinant cells of claim 9, wherein the reporter gene encodes a gene product which confers a growth signal.
13. The recombinant cells of claim 9, wherein the reporter gene encodes a gene product for growth in media containing aminotriazole or canavanine.
14. The recombinant cells of claim 8, wherein the detectable signal comprises intracellular calcium mobilization.
15. The recombinant cells of claim 8, wherein the detectable signal comprises a 1 significant change in intracellular protein phosphorylation.

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16. The recombinant cells of claim 8, wherein the detectable signal comprises increases in phospholipid metabolism.
17. The recombinant cells of claim 8, wherein each cell further comprises a heterologous gene construct encoding the receptor protein.
18. The recombinant cells of claim 8, wherein the receptor protein is a G-protein coupled receptor.
19. The recombinant cells of claim 18, wherein the G-protein coupled receptor is selected from the group consisting of: a chemoattractant peptide receptor, a neuropeptide receptor, a light receptor, a neurotransmitter receptor, a cyclic AMP receptor, and a polypeptide hormone receptor.
20. The recombinant cells of claim 8 wherein the receptor protein is a receptor tyrosine kinase.
21. The recombinant cells of claim 20, wherein the receptor tyrosine kinase is an EPH receptor.
22. The recombinant cells of claim 8, wherein the receptor protein is an orphan receptor.
23. The recombinant cells of claim 8, which recombinant cells are yeast cells.
24. The recombinant cells of claim 8, which recombinant cells are mammalian cells.
25. The recombinant cells of claim 8, wherein the variegated population of test polypeptides includes at least  $10^3$  different test polypeptides.
26. A recombinant cell, comprising:
  - (i) an expressible recombinant gene encoding a heterologous cell surface receptor protein whose signal transduction activity is modulated by extracellular signals;
  - (ii) an expressible recombinant gene encoding a heterologous potential receptor effector polypeptide including a signal sequence for secretion; and
  - (iii) a reporter gene construct containing a reporter gene in operative linkage with one or more transcriptional regulatory elements responsive to the signal

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transduction activity of the cell surface receptor protein.

27. The recombinant cell of claim 26, wherein the reporter gene encodes a gene product that gives rise to a detectable signal selected from the group consisting of: color, fluorescence, luminescence, cell viability relief of a cell nutritional requirement, cell growth, and drug resistance.
28. The recombinant cell of claim 26, wherein the receptor protein is a G-protein coupled receptor.
29. The recombinant cell of claim 28, wherein the G-protein coupled receptor is selected from the group consisting of: a chemoattractant peptide receptor, a neuropeptide receptor, a light receptor, a neurotransmitter receptor, a cyclic AMP receptor, and a polypeptide hormone receptor.
30. The recombinant cell of claim 26, wherein the receptor protein is a receptor tyrosine kinase.
31. The recombinant cell of claim 30, wherein the receptor tyrosine kinase is an EPH receptor.
32. The recombinant cell of claim 26, wherein the receptor protein is an orphan receptor.
33. The recombinant cell of claim 26, wherein the receptor protein is a cytokine receptor.
34. The recombinant cell of claim 26, wherein the receptor protein is an MIRR.
35. The recombinant cell of claim 26, which recombinant cell is a yeast cell.
36. The recombinant cell of claim 35, which yeast cells is a *Saccharomyces* cell.
37. The recombinant cell of claim 35, which yeast cells is a *Schizosaccharomyces* cell.
38. The recombinant cell of claim 26, which cells are mammalian cells.
39. A mixture of recombinant cells, each cell of which comprises:

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- (i) an expressible recombinant gene encoding a heterologous cell surface receptor protein whose signal transduction activity is modulated by extracellular signals;
- (ii) an expressible recombinant gene encoding a heterologous potential receptor effector polypeptide including a signal sequence for secretion; and
- (iii) a reporter gene construct containing a reporter gene in operative linkage with one or more transcriptional regulatory elements responsive to the signal transduction activity of the cell surface receptor protein,

wherein collectively the mixture of cells expresses a variegated population of test polypeptides.

40. The recombinant cells of claim 39, wherein the receptor protein is a G-protein coupled receptor.

41. The recombinant cells of claim 40, wherein the G-protein coupled receptor is selected from the group consisting of: a chemoattractant peptide receptor, a neuropeptide receptor, a light receptor, a neurotransmitter receptor, a cyclic AMP receptor, and a polypeptide hormone receptor.

42. The recombinant cell of claim 40, wherein the G-protein coupled receptor is selected from the group consisting of:  $\alpha$ 1A-adrenergic receptor,  $\alpha$ 1B-adrenergic receptor,  $\alpha$ 2-adrenergic receptor,  $\alpha$ 2B-adrenergic receptor,  $\beta$ 1-adrenergic receptor,  $\beta$ 2-adrenergic receptor,  $\beta$ 3-adrenergic receptor, m1 acetylcholine receptor (AChR), m2 AChR, m3 AChR, m4 AChR, m5 AChR, D1 dopamine receptor, D2 dopamine receptor, D3 dopamine receptor, D4 dopamine receptor, D5 dopamine receptor, A1 adenosine receptor, A2b adenosine receptor, 5-HT1a, 5-HT1b, 5HT1-like, 5-HT1d, 5HT1d-like, 5HT1d beta, substance K (neurokinin A), fMLP receptor, fMLP-like receptor, angiotensin II type 1, endothelin ETA, endothelin ETB, thrombin, growth hormone-releasing hormone (GHRH), vasoactive intestinal peptide, oxytocin, somatostatin SSTR1 and SSTR2, SSTR3, cannabinoid, follicle stimulating hormone (FSH), leutropin (LH/HCG), thyroid stimulating hormone (TSH), thromboxane A2, platelet-activating factor (PAF), C5a anaphylatoxin, Interleukin 8 (IL-8) IL-8RA, IL-8RB, Delta Opioid, Kappa Opioid, mip-1/RANTES, Rhodopsin, Red opsin, Green opsin, Blue opsin, metabotropic glutamate mGluR1-6, histamine H2, ATP, neuropeptide Y, amyloid protein precursor, insulin-like growth factor II, bradykinin, gonadotropin-releasing hormone, cholecystokinin, melanocyte stimulating hormone receptor, antidiuretic hormone receptor, glucagon receptor, and adrenocorticotrophic hormone II.

43. The recombinant cells of claim 39, wherein the receptor protein is a receptor tyrosine kinase.

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44. The recombinant cells of claim 43, wherein the receptor tyrosine kinase is an EPH receptor.

45. The yeast cell of claim 44, wherein the receptor is selected from the group consisting of: *eph*, *elk*, *eck*, *sek*, *mek4*, *hek*, *hek2*, *EEK*, *erk*, *tyro1*, *tyro4*, *tyro5*, *tyro6*, *tyro11*, *cek4*, *cek5*, *cek6*, *cek7*, *cek8*, *cek9*, *cek10*, *bsk*, *rtk1*, *rtk2*, *rtk3*, *myk1*, *myk2*, *ehk1*, *ehk2*, *pagliaccio*, *htk*, *erk* and *nuk* receptors.

46. The recombinant cell of claim 39, wherein the receptor protein is a cytokine receptor.

47. The recombinant cell of claim 39, wherein the receptor protein is an MIRR receptor.

48. The recombinant cell of claim 39, wherein the receptor protein is an orphan receptor.

49. The recombinant cell of claim 39, which recombinant cell is a yeast cell.

50. The recombinant cell of claim 49, which yeast cells is a *Saccharomyces* cell.

51. The recombinant cell of claim 49, which yeast cells is a *Schizosaccharomyces* cell.

52. The recombinant cell of claim 39, which cells are mammalian cells.

53. The recombinant cells of claim 39, wherein the variegated population of test polypeptides includes at least  $10^3$  different test polypeptides.

54. A method for identifying potential receptor effectors comprising:

- (i) providing a mixture of recombinant cells, each cell of which comprises
  - (a) a receptor protein whose signal transduction activity is modulated by interaction with an extracellular signal, and
  - (b) an expressible recombinant gene encoding a heterologous test polypeptide, wherein the mixture of cells collectively express a variegated population of test polypeptides, and modulation of the signal transduction activity of the receptor protein by a test polypeptide provides a detection signal; and
- (ii) isolating cells from the mixture which exhibit the detection signal.

55. The method of claim 54, wherein the cell receptor is a cell surface receptor.
56. The method of claim 55, wherein the heterologous test polypeptide includes a signal sequence for secretion.
57. The method of claim 54, wherein each cell of the mixture further comprises a reporter gene construct containing a reporter gene in operative linkage with one or more transcriptional regulatory elements responsive to the signal transduction activity of the cell surface receptor protein, expression of the reporter gene providing the detection signal.
58. The method of claim 57, wherein the reporter gene encodes a gene product that gives rise to a detection signal selected from the group consisting of: color, fluorescence, luminescence, cell viability relief of a cell nutritional requirement, cell growth, and drug resistance.
59. The method of claim 58, wherein the reporter gene encodes a gene product selected from the group consisting of chloramphenicol acetyl transferase, beta-galactosidase and secreted alkaline phosphatase.
60. The method of claim 58, wherein the reporter gene encodes a gene product which confers a growth signal.
61. The method of claim 58, wherein the reporter gene encodes a gene product for growth in media containing aminotriazole or canavanine.
62. The method of claim 54, wherein the detection signal comprises intracellular calcium mobilization.
63. The method of claim 54, wherein the detection signal comprises a statistically significant change in intracellular protein phosphorylation.
64. The method of claim 54, wherein the detection signal comprises changes in phospholipid metabolism.
65. The method of claim 54, wherein each cell of the mixture further comprises a heterologous gene construct encoding the receptor protein.

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66. The method of claim 54, wherein the receptor protein is a G-protein coupled receptor.
67. The method of claim 66, wherein the G-protein coupled receptor is selected from the group consisting of: a chemoattractant peptide receptor, a neuropeptide receptor, a light receptor, a neurotransmitter receptor, a cyclic AMP receptor, and a polypeptide hormone receptor.
68. The method of claim 54, wherein the receptor protein is a receptor tyrosine kinase.
69. The method of claim 68, wherein the receptor tyrosine kinase is an EPH receptor.
70. The method of claim 54, wherein the receptor protein is a cytokine receptor.
71. The method of claim 54, wherein the receptor protein is an orphan receptor.
72. The method of claim 54, which recombinant cells are yeast cells.
73. The method of claim 54, which recombinant cells are mammalian cells.
74. The method of claim 54, wherein the variegated population of test polypeptides includes at least  $10^3$  different test polypeptides.
75. A method for identifying effectors of a cell surface receptor comprising:
- (i) providing a mixture of recombinant cells, each cell of which comprises
    - (a) an expressible recombinant gene encoding a heterologous cell surface receptor protein whose signal transduction activity is modulated by extracellular signals,
    - (b) an expressible recombinant gene encoding a heterologous potential receptor effector polypeptide including a signal sequence for secretion, and
    - (c) a reporter gene construct containing a reporter gene in operative linkage with one or more transcriptional regulatory elements responsive to the signal transduction activity of the cell surface receptor protein,
- wherein the mixture of cells collectively express a variegated population of test polypeptides, and modulation of the signal transduction activity of the receptor protein by a test polypeptide causes a statistically significant change in the level of expression of the reporter gene; and



(ii) isolating cells from the mixture which exhibit the detection signal.

76. A method for identifying ligands for an orphan cell surface receptor comprising:

- (i) providing a mixture of recombinant cells, each cell of which comprises
  - (a) a heterologous gene encoding an orphan cell surface receptor whose signal transduction activity is modulated by extracellular signals; and
  - (b) an expressible recombinant gene encoding a heterologous test polypeptide including a signal sequence for secretion,

wherein the mixture of cells collectively express a variegated population of test polypeptides, and modulation of the signal transduction activity of the orphan receptor protein by a test polypeptide provides a detection signal; and

(ii) isolating cells from the mixture which exhibit the detection signal.

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